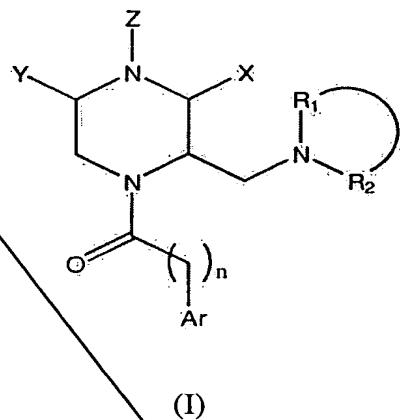


**WHAT IS CLAIMED IS:**

A pharmaceutical composition for the prevention or treatment of pruritus comprising a compound of formula I or a pharmaceutically acceptable salt thereof



5 wherein

n = 1-3;

R<sub>1</sub> and R<sub>2</sub> are independently  $-\text{CH}_3$ ;  $-(\text{CH}_2)_m$ , where m =

4-8,  $-\text{CH}_2\text{CH}(\text{OH})(\text{CH}_2)_2-$ ;  $-\text{CH}_2\text{CH}(\text{F})(\text{CH}_2)_2-$ ;

$-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2-$ ; or  $-(\text{CH}_2)_2\text{CH}=\text{CHCH}_2-$ ;

Ar = unsubstituted or mono-, or di-substituted phenyl

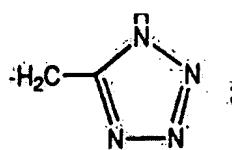
wherein said substituents are selected from the group

consisting of halogen,  $\text{OCH}_3$ ,  $\text{SO}_2\text{CH}_3$ ,  $\text{CF}_3$ , amino, alkyl, and 3,4-dichloro; benzothiophenyl; benzofuranyl; naphthyl; diphenyl methyl; or 9-fluorene;

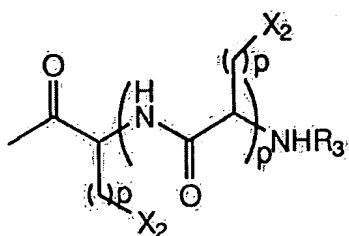
15 Z is

$-\text{P}(\text{O})(\text{OBn})_2$ ;  $-\text{P}(\text{O})(\text{OH})_2$ ;  $-(\text{CH}_2)_p\text{C}(\text{O})\text{NHOH}$ ;  $-(\text{CH}_2)_p\text{CO}_2\text{H}$ ;  $-\text{SO}_2\text{CH}_3$ ;  $-\text{SO}_2\text{NH}_2$ ;  $\text{CO}(\text{CH}_2)_p\text{CH}(\text{NH}_2)(\text{CO}_2\text{H})$ ;  $-\text{COCH}(\text{NH}_2)(\text{CH}_2)_p\text{CO}_2\text{H}$ ;  $-\text{CO}_2\text{CH}_3$ ;  $-\text{CONH}_2$ ;  $-(\text{CH}_2)_p\text{O}(\text{CH}_2)_p\text{CO}_2\text{H}$ ;  $-(\text{CH}_2)_p\text{O}(\text{CH}_2)_p\text{CONHOH}$ ;  $-(\text{CH}_2)_p\text{NHSO}_2\text{CH}_3$ ;  $-(\text{CH}_2)_p\text{NHC}(\text{S})\text{NHCH}(\text{CO}_2\text{H})(\text{CH}_2)_p\text{CO}_2\text{H}$ ;  $-(\text{CH}_2)_p\text{SO}_3\text{H}$ ; or

or Z is



wherein



$$p = 0 - 20$$

$R_3 = -H$  or  $-Ac$ ;

$X_2 = -CO_2H$ ;  $-NHSO_2CH_3$ ;  $NHP(O)(OBn)_2$ ;  $NHP(O)(OH)_2^-$ ;  
 $OP(O)(OBn)_2$ ; or  $OP(O)(OH)_2$

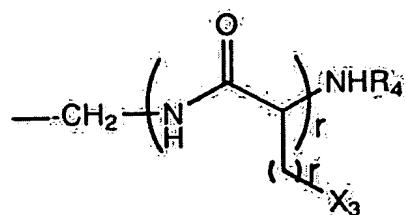
X and Y are independently

$-CH_2NHSO_2CH_3$ ,  $-CH_2NHP(O)(OBn)_2$ ,  $-CH_2NHRO(OH)_2$ , -

$CH_2OP(O)(OBn)_2$ ,  $CH_2OP(O)(OH)_2$ ,  $(CH_2)_qO(CH_2)_qCO_2H$ ,

$(CH_2)_qO(CH_2)_qSO_3H$ ,  $(CH_2)_qO(CH_2)_qCHNHOH$ ,

$CH_2NHC(S)NHCH(CO_2H)(CH_2)_qCO_2H$ , or



~~wherein~~

~~q = 1-20~~

~~r = 1-20~~

~~R<sub>4</sub> = -H or-Ac~~

- 5 X<sub>3</sub> = -CO<sub>2</sub>H; -NHSO<sub>2</sub>CH<sub>3</sub>; -NHP(O)(OBn)<sub>2</sub>;  
           -NHP(O)(OH)<sub>2</sub>; -OP(O)(OBn)<sub>2</sub>; or  
           -OP(O)(OH)<sub>2</sub>

in a pharmaceutically acceptable carrier.

2. The pharmaceutical composition according to claim 1 wherein said compound is selected from the group consisting of: (4-[1-(3,4-Dichlorophenyl)acetyl-2R-(1-pyrrolidinyl)-methyl]piperazinyl)acetic acid; [1-(3,4-Dichlorophenyl)acetyl-4-methanesulfonyl-2R-(1-pyrrolidinyl)methyl]piperazine; [4-S-Aspartic acid- $\alpha$ -amido-1-(3,4-dichlorophenyl)acetyl-2R-(1-pyrrolidinyl)methyl]piperazine; Methyl-[2R-(O-2-acetic acid)hydroxymethyl-4-(3,4-dichlorophenyl)acetyl-3R-(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate; Methyl-[2R-(O-S-aspartic acid- $\alpha$ -acetyl)hydroxymethyl-4-(3,4-dichlorophenyl)acetyl-3R-(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate; Methyl-[4-(3,4-dichlorophenyl)acetyl-2R-(N-methanesulfonamido)aminomethyl-3R-(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate; Methyl-{4-[3,4-dichlorophenyl]acetyl-3R-[1-pyrrolidinyl]methyl-2R-[N-(succinic acid-2S-thioureido)aminomethyl-1-piperazinecarboxylate; Methyl-[2S-(O-2-acetic acid)hydroxymethyl-4-(3,4-dichlorophenyl)acetyl-5R-(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate; Methyl-[2S-(O-S-aspartic acid- $\alpha$ -acetyl)hydroxymethyl-4-(3,4-dichlorophenyl)acetyl-5R-(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate; Methyl-[4-(3,4-dichlorophenyl)acetyl-2S-(N-methanesulfonamido)aminomethyl-5R-(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate; Methyl-{4-[3,4-dichlorophenyl]acetyl-5R-[1-pyrrolidinyl]methyl}-2S-[N-(succinic acid-2S-thioureido)aminomethyl-1-piperazinecarboxylate; Methyl-[2R-(O-2-acetic acid)hydroxymethyl-4-(3,4-dichlorophenyl)acetyl-5R-(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate; Methyl-[2R-(O-S-aspartic acid- $\alpha$ -acetyl)hydroxymethyl-4-(3,4-dichlorophenyl)acetyl-5R-(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate; Methyl-[4-(3,4-dichlorophenyl)acetyl-2R-(N-methanesulfonamido)aminomethyl-5R-(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate; and Methyl-{4-[3,4-dichlorophenyl]acetyl-5R-[1-pyrrolidinyl]methyl-2R-[N-(succinic acid-2S-thioureido)aminomethyl]-1-piperazinecarboxylate.

3. The pharmaceutical composition according to claim 1 wherein said compound is selected from the group consisting of:

- (R)-4-(Phenylmethyl)-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]piperazine hydrochloride;
- (R)-1-[(3,4-Dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]piperazine hydrochloride;
- (R)-4-Methanesulfonyl-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine hydrochloride;
- (R)-4-t-Butyl-acetyl-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]- piperazine;
- (R)-4-(3,4-Dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazineacetic acid dihydrochloride;
- (R)-4-N-t-Boc-D-aspartic acid- $\beta$ -benzyl ester-1 -[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine;
- (R)-4-Aspartic acid-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine dihydrochloride;
- (R)-4-Acetyl-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine hydrochloride;
- (R)-4-(Diethoxyphosphonate)-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine hydrochloride;
- (R)-4-Trifluoroacetyl-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine hydrochloride;
- (R)-4-[(3,4-Dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazinecarboxamide hydrochloride;
- (R)-4-[(3,4-Dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazinecarboxaldehyde hydrochloride;
- (R)-4-[(3,4-Dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazine-sulfonamide hydrochloride;
- (R)-4-(4-Methylphenylsulfonyl)-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl] -piperazine hydrochloride;

(*R,S*)-4-Methanesulfonyl-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine hydrochloride;

(*R,S*)-4-Methanesulfonyl-1-[(4-methylsulfonylphenyl)acetyl]-2-[(1-pyrrolidinyl)-methyl]piperazine hydrochloride;

5 (*R,S*)-4-Methanesulfonyl-1-[(2-nitrophenyl)acetyl]-2-[(1-pyrrolidinyl)-methyl]piperazine hydrochloride;

(*R,S*)-4-Methanesulfonyl-1-[(4-trifluoromethylphenyl)acetyl]-2-[(1-pyrrolidinyl)-methyl]piperazine hydrochloride;

10 (*R,S*)-4-Methanesulfonyl-1-[(3-indolylacetyl)-2-[(1-pyrrolidinyl)-methyl]piperazine hydrochloride;

(*R,S*)-Methyl 4-[(4-methylsulfonylphenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-1-piperazinecarboxylate hydrochloride;

(*R,S*)-Methyl 4-[(4-trifluoromethylphenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-1-piperazinecarboxylate hydrochloride;

15 (*R,S*)-Methyl 4-[(3-indolyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-1-piperazine-carboxylate hydrochloride;

(*R,S*)-Methyl 4-[(2-nitrophenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-1-piperazine-carboxylate hydrochloride;

20 (*R,S*)-Methyl 4-[(2-methoxyphenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-1-piperazine-carboxylate hydrochloride;

(*R,S*)-Methyl 4-[(2-aminophenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-1-piperazine-carboxylate dihydrochloride;

(*R,S*)-4-Acetyl-1-[(4-methylsulfonylphenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-piperazine hydrochloride;

25 (*R,S*)-4-Acetyl-1-(4-trifluoromethylphenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]piperazinecarboxylate hydrochloride;

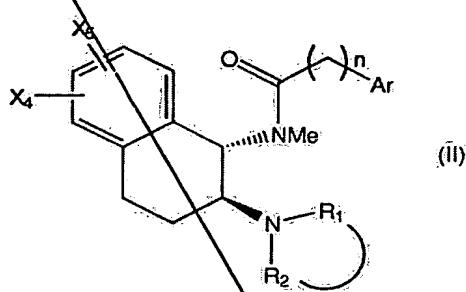
(*R,S*)-4-Acetyl-1-[(2-trifluoromethylphenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]piperazinecarboxylate hydrochloride;

(*R,S*)-4-Acetyl-1-[(3-nitrophenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]piperazine-carboxylate hydrochloride;

(*R,S*)-4-Acetyl-1-[(2-nitrophenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]piperazine-carboxylate hydrochloride;

5 (*R,S*)-4-Acetyl-1-[(4-nitrophenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]piperazine; carboxylate hydrochloride; and

(*R,S*)-4-(Phenylmethyl)-1-[(4,5,-dichloro-2-nitrophenyl)acetyl]-2-[(1-



pyrrolidinyl)methyl]piperazine dihydrochloride.

4. A method for the prevention or treatment of pruritus in a patient comprising administering to said patient an effective amount of a composition according to claim 1.

5. A method for the prevention or treatment of pruritus in a patient comprising administering to said patient an effective amount of a composition according to claim 2.

6. A method for the prevention or treatment of pruritus in a patient comprising administering to said patient an effective amount of a composition according to claim 3.

15 7. A pharmaceutical composition for the prevention or treatment of pruritus comprising a compound of formula II or a pharmaceutically acceptable salt thereof wherein

$$n = 1-3;$$

20  $R_1$  and  $R_2$  are independently  $= CH_3 ; -(CH_2)_m$ , where  $m =$

$4-8$ ,  $-CH_2CH(OH)(CH_2)_2$ ;  $-CH_2CH(F)(CH_2)_2$ ;

$-(CH_2)_2O(CH_2)_2$ ; or  $-(CH_2)_2CH=CHCH_2$ ;

Ar = unsubstituted or mono-, or di-substituted phenyl wherein said substituents are selected from the group consisting of halogen,  $OCH_3$ ,  $SO_2CH_3$ ,  $CF_3$ , amino, alkyl, and 3,4-dichloro; benzothiophenyl; benzofuranyl; naphthyl; diphenyl methyl; or 9-fluorene;

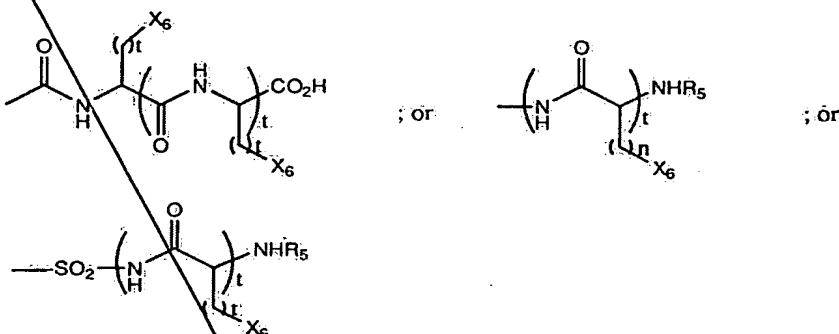
25

X<sub>4</sub> and X<sub>5</sub> are independently

-OP(O)(OBn)<sub>2</sub>; -OP(O)(OH);; -CO<sub>2</sub>H; -SO<sub>3</sub>H; -O(CH<sub>2</sub>)<sub>n</sub>CO<sub>2</sub>H;  
-NHSO<sub>2</sub>CH<sub>3</sub>; -CONH(CH<sub>2</sub>)<sub>s</sub>CO<sub>2</sub>H; or -SO<sub>2</sub>NH(CH<sub>2</sub>)<sub>s</sub>CO<sub>2</sub>H; wherein

s = 1-5

5 or X<sub>4</sub> and X<sub>5</sub> are independently



10 wherein

t = 1-20

15 R<sub>5</sub>=-H or-Ac

X<sub>6</sub> = -CO<sub>2</sub>H; -NHSO<sub>2</sub>CH<sub>3</sub>; -NHP(O)(OBn)<sub>2</sub>; -NHP(O)(OH)<sub>2</sub>; -OP(O)(OBn)<sub>2</sub>; or  
-OP(O)(OH)<sub>2</sub>

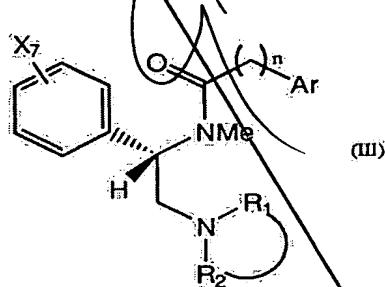
in a pharmaceutically acceptable carrier.

8. The pharmaceutical composition according to claim 7 wherein said compound is selected from the group consisting of: ( $\pm$ )-2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-5-(O-2-acetic acid)-hydroxy-2-(1-pyrrolidinyl)naphthyl]acetamide; ( $\pm$ )-2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-7-(O-2-acetic acid)-hydroxy-2-(1-pyrrolidinyl)naphthyl]acetamide; ( $\pm$ )-2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-7-(N-methanesulfonamido)-amino-2-(1-pyrrolidinyl)naphthyl]acetamide; ( $\pm$ )-2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-5-(N-methanesulfonamido)-amino-2-(1-pyrrolidinyl)naphthyl]acetamide; ( $\pm$ )-2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-5-(N-2-acetic acid)-carboxamido-2-(1-pyrrolidinyl)naphthyl]acetamide; ( $\pm$ )-2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-7-(N-2-acetic acid)-sulfonamido-2-(1-pyrrolidinyl)naphthyl]acetamide; ( $\pm$ )-2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-7-(N-2-acetic acid)-carboxamido-2-(1-pyrrolidinyl)naphthyl]acetamide; and ( $\pm$ )-2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-7-(N-2-acetic acid)-sulfonamido-2-(1-pyrrolidinyl)naphthyl]acetamide.

9. The pharmaceutical composition according to claim 7 wherein said compound is selected from the group consisting of:

- 2-(7-[ $\pm$ ]-trans-1-(N-3,4-dichlorophenylacetamido-N-methylamino)-2-(1-pyrrolidinyl)-1,2,3,4-tetrahydronaphthoxy} acetic acid;
- 2,2-Diphenyl-N-methyl-N-[ $\pm$ -trans-2-(1-pyrrolidinyl)-7-methoxy-1,2,3,4-tetrahydronaphth-1-yl]acetamide;
- 5 2,2-Diphenyl-N-methyl-N-[ $\pm$ -trans-2-(1-pyrrolidinyl)-7-hydroxy-1,2,3,4-tetrahydronaphth-1-yl]acetamide;
- 2-(2-Nitro-4,5-dichlorophenyl)-N-methyl-N-[ $\pm$ -trans-2-(1-pyrrolidinyl)-7-nitro-1,2,3,4-tetrahydronaphth-1-yl]acetamide;
- 10 2-(3,4-Dichlorophenyl)-N-methyl-N-[ $\pm$ -trans-2-(1-pyrrolidinyl)-7-nitro-1,2,3,4-tetrahydronaphth-1-yl]acetamide;
- 2-(3,4-Dichlorophenyl)-N-methyl-N-[ $\pm$ -trans-2-(1-pyrrolidinyl)-7-amino-1,2,3,4-tetrahydronaphth-1-yl]acetamide;
- 15 2-(4-Methylsulfonylphenyl)-N-methyl-N-[ $\pm$ -trans-2-(1-pyrrolidinyl)-7-nitro-1,2,3,4-tetrahydronaphth-1-yl]acetamide;
- 2-(3,4-Dichlorophenyl)-N-methyl-N-[ $\pm$ -trans-2-[1-pyrrolidinyl]-7-[N,N-bis-(t-butoxycarbonylmethyl)-amino]-1,2,3,4-tetrahydronaphth-1-yl]acetamide;
- 20 2-(3,4-Dichlorophenyl)-N-methyl-N-[ $\pm$ -trans-2-[1-pyrrolidinyl]-7-[N,N-bis-(carboxymethyl)amino]-1,2,3,4-tetrahydronaphth-1-yl]acetamide;
- 2-(3,4-Dichlorophenyl)-N-methyl-N-[ $\pm$ -trans-2-[1-pyrrolidinyl]-7-[N,N-bis-(ethoxycarbonylmethyl)-amino]-1,2,3,4-tetrahydronaphth-1-yl]acetamide;
- 25 2-(3,4-Dichlorophenyl)-N-methyl-N-[ $\pm$ -trans-2-(1-pyrrolidinyl)-7-(N-diethylphosphoramido-amino)-1,2,3,4-tetrahydronaphth-1-yl]acetamide;
- 2-(3,4-Dichlorophenyl)-N-methyl-N-[ $\pm$ -trans-2-[1-pyrrolidinyl]-7-[N-2-(diethylphosphoryl)ethyl-amino]-1,2,3,4-tetrahydronaphth-1-yl]acetamide;
- 2-(3,4-Dichlorophenyl)-N-methyl-N-[ $\pm$ -trans-2-(1-pyrrolidinyl)-6-methoxy-7-(N-benzyl-N-methylaminosulfonyl)-1,2,3,4-tetrahydronaphth-1-yl]acetamide;
- 2-(3,4-Dichlorophenyl)-N-methyl-N-[ $\pm$ -trans-2-(1-pyrrolidinyl)-7-(N-benzyl-N-methylaminosulfonyl)-1,2,3,4-tetrahydronaphth-1-yl]acetamide;

- ~~2-(2-Nitro-4,5-dichlorophenyl)-N-methyl-N-[ $(\pm)$ -trans-2-(1-pyrrolidinyl)-indan-1-yl]acetamide;~~
- ~~2-(2-Nitro-4-trifluoromethylphenyl)-N-methyl-N-[ $(\pm)$ -trans-2-(1-pyrrolidinyl)-indan-1-yl]acetamide;~~
- 5 2,2-Diphenyl-N-methyl-N-[ $(\pm)$ -trans-2-(1-pyrrolidinyl)-indan-1-yl]acetamide; and  
~~2-(4-Methylsulfonylphenyl)-N-methyl-N-[ $(\pm)$ -trans-2-(1-pyrrolidinyl)-indan-1-yl]acetamide.~~
- 10 10. A method for the prevention or treatment of pruritus in a patient comprising administering to said patient an effective amount of a composition according to claim 7.
11. A method for the prevention or treatment of pruritus in a patient comprising  
10 administering to said patient an effective amount of a composition according to claim 8.
12. A method for the prevention or treatment of pruritus in a patient comprising administering to said patient an effective amount of a composition according to claim 9.
13. A pharmaceutical composition for the prevention or treatment of pruritus comprising a compound of the formula III or a pharmaceutically acceptable salt thereof



15 wherein

$$n = 1-3;$$

R<sub>1</sub> and R<sub>2</sub> are independently = CH<sub>3</sub>; -(CH<sub>2</sub>)<sub>m</sub>, where m = 4-8,  
-CH<sub>2</sub>CH(OH)(CH<sub>2</sub>)<sub>2</sub>; -CH<sub>2</sub>CH(F)(CH<sub>2</sub>)<sub>2</sub>; -(CH<sub>2</sub>)<sub>2</sub>O(CH<sub>2</sub>)<sub>2</sub>; or  
-(CH<sub>2</sub>)<sub>2</sub>CH=CHCH<sub>2</sub>;

20 Ar = unsubstituted or mono-, or di-substituted phenyl wherein said substituted are selected from the group consisting of halogen, OCH<sub>3</sub>, SO<sub>2</sub>CH<sub>3</sub>, CF<sub>3</sub>, amino, alkyl, and 3,4-dichloro; benzothiophenyl; benzofuranyl; naphthyl; diphenyl methyl; or 9-fluorene;

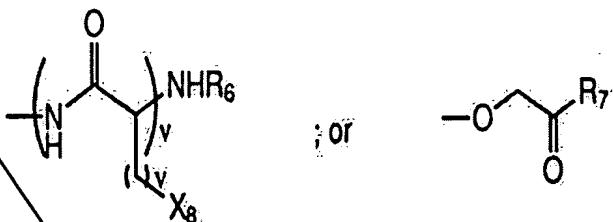
X<sub>7</sub> is

25 -NHSO<sub>2</sub>CH<sub>3</sub>; -NHP(O)(OBn)<sub>2</sub>; -NHP(O)(OH)<sub>2</sub>; -(CH<sub>2</sub>)<sub>u</sub>NHSO<sub>2</sub>CH<sub>3</sub>;  
-(CH<sub>2</sub>)<sub>u</sub>NHC(S)NHCH(CO<sub>2</sub>H)(CH<sub>2</sub>)<sub>u</sub>CO<sub>2</sub>H; -CONHOH; or -(CH<sub>2</sub>)<sub>u</sub>CONHOH;

wherein

$u = 1-5$ ; or

$X_7$  is



$R_6 = -\text{H}$  or  $-\text{Ac}$ ;

$X_8 = -\text{CO}_2\text{H}; -\text{NHSO}_2\text{CH}_3; -\text{NHP(O)(OBn)}_2;$

$-\text{NHP(O)(OH)}_2; \text{OP(O)(OBn)}_2$  or

$-\text{OP(O)(OH)}_2;$

$R_7 = -\text{NH}(\text{CH}_2)_v\text{CO}_2\text{H}; -$

$\text{NH}(\text{CH}_2)_v\text{CH}(\text{NH}_2)(\text{CO}_2\text{H});$

$-\text{NHCH}(\text{CO}_2\text{H})(\text{CH}_2)_v\text{NH}_2; \text{NH}(\text{CH}_2)_v\text{SO}_3\text{H}_2;$

$-\text{NH}(\text{CH}_2)_v\text{PO}_3\text{H}_2; -$

$\text{NH}(\text{CH}_2)_v\text{NHC(NH)NH}_2;$  or

$-\text{NHCH}(\text{CO}_2\text{H})(\text{CH}_2)_v\text{CO}_2\text{H};$  and

$v = 1-20;$

5 in a pharmaceutically acceptable carrier.

14. The pharmaceutical composition according to claim 13 wherein said compound is selected from the group consisting of:

2-(3,4-dichlorophenyl)-N-methyl-N-(1-[3-(N-2-acetic acid)carboxamido]phenyl-2-(1-pyrrolidinyl)ethyl)acetamide; 2-(3,4-dichlorophenyl)-N-methyl-N-1-[3-(N-

10 methanesulfonamido)aminomethyl]phenyl-2-(1-pyrrolidinyl)ethyl)acetamide; 2-(3,4-dichlorophenyl)-N-methyl-N-(1-[3-(N-succinic acid-2S-thioureido)aminomethyl]phenyl-2-(1-pyrrolidinyl)ethyl)acetamide; and 2-(3,4-dichlorophenyl)-N-methyl-N-(1-[3-(N-2-acetic acid)sulfonamido]phenyl-2-(1-pyrrolidinyl)ethyl)acetamide.

15. The pharmaceutical composition according to claim 13 wherein said compound is

15 selected from the group consisting of:

- 2-(3,4-Dichlorophenyl)-N-methyl-N-[(1S)-1-[N-(S-aspartic acid- $\alpha$ -amide-S-aspartic acid-a-amido)-3-aminophenyl]-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(3,4-Dichlorophenyl)-N-methyl-N-[(1S)-1-[N-(bis-methylsulfonamido)-3-aminophenyl]-2-(1-pyrrolidinyl)ethyl]acetamide;
- 5 2-(2-Nitrophenyl)-N-methyl-N-[(1S)-1-(3-nitrophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(2-Aminophenyl)-N-methyl-N-[(1S)-1-(3-aminophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(N-Diethyl phosphoramidate-2-aminophenyl)-N-methyl-N-[(1S)-1-(N-diethyl phosphoramidate-3-aminophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(N-Bis-sulfonamido-2-aminophenyl)-N-methyl-N-[(1S)-1-(N-bis-sulfonamido-3-aminophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;
- 10 2-(2-Nitro-4,5-dichlorophenyl)-N-methyl-N-[(1S)-1-(3-nitrophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(4-Methylsulfonylphenyl)-N-methyl-N-[(1S)-1-(3-nitrophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;
- 15 2-(N-Butyloxycarbonyl-4-aminophenyl)-N-methyl-N-[(1S)-1-(3-nitrophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(4-Aminophenyl)-N-methyl-N-[(1S)-1-(3-nitrophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(N-Bis-sulfonamido-4-aminophenyl)-N-methyl-N-[(1S)-1-(3-nitrophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;
- 20 2-(N-Bis-sulfonamido-4-aminophenyl)-N-methyl-N-[(1S)-1-(3-aminophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(N-Bis-sulfonamido-4-aminophenyl)-N-methyl-N-[(1S)-1-(N-diethyl phosphoramidate-3-aminophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;
- 25 2-(2-Nitrophenyl)-N-methyl-N-[(1S)-1-phenyl-2-[1-(3S)-(3-hydroxypyrrolidinyl)]ethyl]acetamide;
- 2-(2-Nitro-4,5-dichlorophenyl)-N-methyl-N-[(1S)-1-phenyl-2-[1-(3S)-(3-hydroxypyrrolidinyl)]ethyl]acetamide;

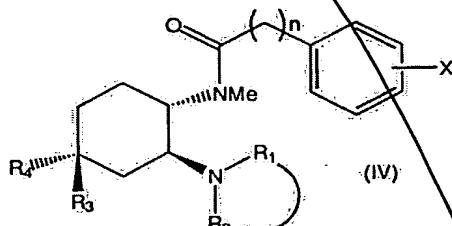
- (2-(4-Methylsulfonylphenyl)-N-methyl-N-[(1S)-1-phenyl-2-[1-(3S)-(3-hydroxypyrrolidinyl)]ethyl]acetamide;
- 2-(2-Nitro-4-trifluoromethylphenyl)-N-methyl-N-[(1S)-1-phenyl-2-[1-(3S)-(3-hydroxypyrrolidinyl)]ethyl]acetamide;
- 5 2-(2-Amino-4-trifluoromethylphenyl)-N-methyl-N-[(1S)-1-phenyl-2-[1-(3S)-(3-hydroxypyrrolidinyl)]ethyl]acetamide;
- 2,2-Diphenyl-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- N',N'-Diphenyl-N-methyl-N-[(1 S)-1-phenyl-2-(1-pyrrolidinyl)ethyl] urea;
- 2-(2-Nitrophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 10 2-(2-Nitro-4,5-dichlorophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(4-Methylsulfonylphenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(2-Methoxyphenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(3-Indolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 15 2-( $\alpha,\alpha,\alpha$ -Trifluoro-p-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(2-Nitro- $\alpha,\alpha,\alpha$ -Trifluoro-4-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(1-[4-Chlorobenzoyl]-5-methoxy-2-methyl indole)-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 20 2-(4-Nitrophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(3-Nitrophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(2-Pyridyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(3-Pyridyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-((+)-6-Methoxy-a-methyl-2-naphthalene)-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 25 2-( $\alpha,\alpha,\alpha$ -Trifluoro-3-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

- 2-(4-Pyridyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-( $\alpha,\alpha,\alpha$ -Trifluoro-2-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-((S)-(+)-4-Isobutyl-x-methylphenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 5 2-(3,4,5-Trimethoxyphenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(2-Aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(2-N,N-Dimethylsulfonamido-2-aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(N-Methylsulfonamido-2-aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 10 2-(2-Amino 4,5-dichlorophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(N,N-Dimethylsulfonamido-2-amino-4,5-dichlorophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide; 2-
- 15 2-(2-Amino,x,x,x-Trifluoro-4-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(2-N,N-Dimethylsulfonamido-2-amino- $\alpha,\alpha,\alpha$ -trifluoro-4-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 20 2-(N-Methylsulfonamido-2-amino- $\alpha,\alpha,\alpha$ -trifluoro-4-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(2-Aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(4-Aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(N,N-Dimethylsulfonamido-2-aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 25 2-(N,N-Dimethylsulfonamido-2-aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

~~2-(2-Hydroxyphenyl)-N-methyl-N-methyl-N-[(1S)-l-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide; and~~

~~N-Methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidine-1-yl)ethyl]-3,4,5-trimethoxyphenylacetamide.~~

- 5 16. A method for the prevention or treatment of pruritus in a patient comprising  
administering to said patient an effective amount of a composition according to claim 13.
17. A method for the prevention or treatment of pruritus in a patient comprising  
administering to said patient an effective amount of a composition according to claim 14.
18. A method for the prevention or treatment of pruritus in a patient comprising  
10 administering to said patient an effective amount of a composition according to claim 15
19. A pharmaceutical composition for the prevention or treatment of pruritus comprising  
a compound of the formula IV or a pharmaceutically acceptable salt thereof



wherein

15 n = 1-3;

R<sub>1</sub> and R<sub>2</sub> are independently = CH<sub>3</sub>; -(CH<sub>2</sub>)<sub>m</sub>, where m =

4-8, -CH<sub>2</sub>CH(OH)(CH<sub>2</sub>)<sub>2</sub>-; -CH<sub>2</sub>CH(F)(CH<sub>2</sub>)<sub>2</sub>-;

-(CH<sub>2</sub>)<sub>2</sub>O(CH<sub>2</sub>)<sub>2</sub>-; or -(CH<sub>2</sub>)<sub>2</sub>CH=CHCH<sub>2</sub>-;

R<sub>3</sub> and R<sub>4</sub> are independently H; OCH<sub>3</sub> alkyl; or c-O(CH<sub>2</sub>)<sub>2</sub>

20 X<sub>9</sub> = 1-4 substituents selected from the groups consisting of

-halogen; -CF<sub>3</sub>; -OCH<sub>3</sub>; -SO<sub>2</sub>NH(CH<sub>2</sub>)<sub>q</sub>CO<sub>2</sub>H; CONH(CH<sub>2</sub>)<sub>q</sub>CO<sub>2</sub>H;

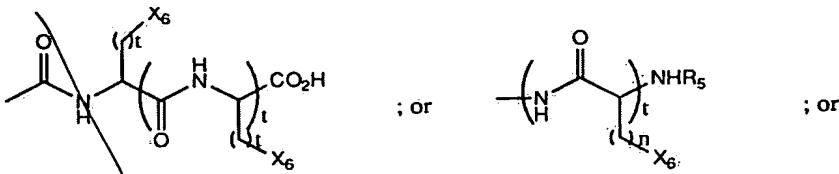
-NH<sub>2</sub>; -NHSO<sub>2</sub>CH<sub>3</sub>; -NHP(O)(OBn)<sub>2</sub>; -NHP(O)(OH)<sub>2</sub>; NH(CH<sub>2</sub>)<sub>q</sub>CO<sub>2</sub>H; -SO<sub>2</sub>CH<sub>3</sub>

-OP(O)(OBn)<sub>2</sub>; -OP(O)(OH)<sub>2</sub>; -CO<sub>2</sub>H; O(CH<sub>2</sub>)<sub>q</sub>CO<sub>2</sub>H; -O(CH<sub>2</sub>)<sub>q</sub>SO<sub>3</sub>H; ;

-O(CH<sub>2</sub>)<sub>q</sub>OPO<sub>3</sub>H<sub>2</sub>; wherein

25 q = 1-20;

or X<sub>9</sub> is



wherein

t = 1-20;

$R_5 = -H$  or  $-Ac$ ;

$X_5 = -CO_2H; -NHSO_2CH_3; -NHP(O)(OBn)_2;$

-NHP(O)(OH)<sub>2</sub>; -OP(O)(OBn)<sub>2</sub>; or  
-OP(O)(OH)<sub>2</sub>

in a pharmaceutically acceptable vehicle.

20. The pharmaceutical composition according to claim 19 wherein said compound is selected from the group consisting of:

10 (-)-(5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro-[4,5]dec-8-yl]-3-(N-methanesulfonamido)aminophenylacetamide; (-)-(5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro-[4,5]dec-8-yl]-3-(N-2-acetic acid)sulfonamidophenylacetamide; and (-)-(5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro-[4,5]dec-8-yl]-3-(N-2-acetic acid)carboxamidophenylacetamide.

15 21. The pharmaceutical composition according to claim 19 wherein said compound is selected from the group consisting of:

( $\pm$ )-*trans*-2-Nitro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]phenylacetamide

## Hydrochloride;

( $\pm$ )-*trans*-2-Amino-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]phenylacetamide

## 20 Hydrochloride;

( $\pm$ )-*trans*-2-Nitro-4,5-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

( $\pm$ )-*trans*-2-Amino-4,5-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

25 ( $\pm$ )-*trans*-2-Methanesulfonamido-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

N-[2-( $\pm$ )-*trans*-N-Methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamido]glycine  
Hydrochloride;  
( $\pm$ )-*trans*-4-Trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide  
Hydrochloride;

5    ( $\pm$ )-*trans*-2-Nitro-4-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-  
phenylacetamide Hydrochloride;  
( $\pm$ )-*trans*-2-Amino-4-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-  
phenylacetamide Hydrochloride;

10    ( $\pm$ )-*trans*-2-Bismethanesulfonamido-4-trifluoromethyl-N-methyl-N-[2-(1-  
pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;  
( $\pm$ )-*trans*-2-Methanesulfonamido-4-trifluoromethyl-N-methyl-N-[2-(1-  
pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

15    N-[2-( $\pm$ )-*trans*-4-Trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-  
phenylacetamido]glycine Hydrochloride;

20    ( $\pm$ )-*trans*-3-Trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide  
Hydrochloride;  
( $\pm$ )-*trans*-5-Nitro-3-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-  
phenylacetamide Hydrochloride;  
( $\pm$ )-*trans*-2-Nitro-3-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-  
phenylacetamide Hydrochloride;

25    ( $\pm$ )-*trans*-2-Trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide  
Hydrochloride;  
( $\pm$ )-*trans*-4-Nitro-2-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-  
phenylacetamide Hydrochloride;

30    ( $\pm$ )-*trans*-4-Amino-2-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-  
phenylacetamide Hydrochloride;  
( $\pm$ )-*trans*-N-Methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]2,2-diphenylacetamide Hydrochloride;  
and  
( $\pm$ )-*trans*-4-Methylsulfonyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]phenylacetamide  
Hydrochloride.

22. A method for the prevention or treatment of pruritus in a patient comprising  
administering to said patient an effective amount of a composition according to claim 19.

23. A method for the prevention or treatment of pruritus in a patient comprising  
administering to said patient an effective amount of a composition according to claim 20.

24. A method for the prevention or treatment of pruritus in a patient comprising administering to said patient an effective amount of a composition according to claim 21.

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